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Carotuximab in combination with pazopanib for advanced angiosarcoma

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LAY SUMMARY

Soft tissue sarcomas are a type of rare cancer that affect tissues that connect, support and surround organs (for example muscle, blood vessels, nerves and tendons). Angiosarcoma is a type of soft tissue sarcoma that develops from blood vessel cells, most commonly in the skin, breast, liver, spleen, and in the deep tissues of the body. In rare cases, angiosarcoma can occur in the heart. Soft tissue sarcomas occur in children and adults of all ages, but most often in middle aged and older adults. People aged 65 years and over have the lowest survival rates. Surgery accompanied by radiotherapy is often the standard treatment. Surgery may not be possible in advanced angiosarcoma and patients may require chemotherapy with limited treatment options.

Carotuximab is a novel, monoclonal antibody (a type of protein) being developed as an intravenous infusion to be added on to oral pazopanib, a current treatment for certain types of soft tissue sarcomas. Carotuximab acts by blocking a specific pathway to slow the growth of the tumour blood vessels, along with growth of the tumour itself. Pazopanib blocks a different pathway that also leads to slowing the growth of tumour blood vessels. Both carotuximab and pazopanib complement each other's action and there is a potential for a more improved clinical treatment and response. If licenced, the combination of carotuximab with pazopanib will provide a treatment option for people with advanced angiosarcoma who cannot have surgery and currently have limited treatment options.

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TARGET GROUP

Advanced angiosarcoma not amenable to surgery, in combination with pazopanib (Votrient).

TECHNOLOGY

DESCRIPTION

Carotuximab (TRC105) is a novel, monoclonal antibody to endoglin (CD105), a protein which is essential for new blood vessel formation (angiogenesis) and is overexpressed on proliferating endothelial cells. Endoglin is also expressed directly on tumour cells in angiosarcoma and is upregulated following vascular endothelial growth factor (VEGF) inhibition. Carotuximab inhibits angiogenesis, tumour growth and metastases.[1, 2]

Pazopanib is an oral inhibitor of multiple receptor tyrosine kinases, including VEGF receptor (VEGFR)-1, VEGFR-2, and VEGFR-3 at therapeutic plasma concentrations. These receptors are implicated in pathologic angiogenesis, tumour growth, and cancer progression.[2] It is indicated for the treatment of adult patients with selective subtypes of advanced soft-tissue sarcoma (STS) who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo) adjuvant therapy.[3]

Carotuximab in combination with pazopanib is in clinical development for patients with angiosarcoma not amenable to curative intent surgery who have not received pazopanib or carotuximab previously. In the phase III clinical trial (TAPPAS; NCT02979899), carotuximab is administered by intravenous (IV) infusion at 10 mg/kg weekly in combination with 800mg (for aged 18+) or 600mg (for aged 12-17) of oral pazopanib. Duration of treatment is not reported.[4]

Carotuximab does not currently have Marketing Authorisation in the EU for any indication.

Carotuximab is in phase II development for the following indications:[5]

- Renal cell cancer (with axitinib)
- Prostate cancer (with abiraterone or enzalutamide)
- Hepatocellular cancer (with sorafenib)
- Breast cancer (with letrozole and everolimus)
- Age-Related Macular Degeneration (ophthalmic formulation DE-122)

INNOVATION and/or ADVANTAGES

Carotuximab is the first product specifically for the treatment of angiosarcoma. There are few effective therapies available, other than chemotherapy or radiotherapy, for soft tissue sarcoma patients for whom surgery is impossible. By targeting a non-VEGF pathway that is upregulated following VEGF inhibition, carotuximab has the potential to complement VEGFR tyrosine kinase inhibitors (TKIs) such as pazopanib, and could represent a major advance in the treatment of angiosarcoma. Together, the use of carotuximab with pazopanib may result in more effective angiogenesis inhibition and improved clinical efficacy over that seen with pazopanib alone.[2]

DEVELOPER

TRACON Pharmaceuticals Inc.

REGULATORY INFORMATION/ MARKETING PLANS

Carotuximab is a designated orphan drug in the EU and USA for soft tissue sarcoma.[6, 7]

PATIENT GROUP

BACKGROUND

Sarcomas are a group of rare cancers that make up around 1% of all adult cancers.[8] Soft tissue sarcomas affect tissues that connect, support and surround organs (for example muscle, blood vessels, nerves and tendons). They can appear in any part of the body, but more occur in the limbs than anywhere else (25%).[9]

Angiosarcoma is a type of soft tissue sarcoma that develops in the blood vessel cells, most commonly in the skin, breast, liver, spleen, and in the deep tissues of the body.[10] Cutaneous angiosarcoma accounts for around 60% of diagnosed angiosarcomas; they are more common in older men and usually appear on the head or neck. Up to 25% of angiosarcomas are soft tissue tumours, which may occur at any age in men or women equally.[11]

The cause of most sarcomas is unknown, but known risk factors include age, some genetic conditions (such as neurofibromatosis type 1 and retinoblastoma), previous radiotherapy (even many years after the exposure),[12] and exposure to certain chemicals such as dioxins and phenoxyacetic herbicides. The most widely known cause of angiosarcoma is lymphoedema, the swelling of an area of the body due to the collection of fluid.[11]

Soft tissue sarcomas often have no obvious symptoms in the early stages, and the symptoms depend on the location in the body. Angiosarcoma can resemble a skin infection or a bruise or lesion that does not heal. It can also present as a soft lump that can be felt or seen.

CLINICAL NEED and BURDEN OF DISEASE

Soft tissue sarcomas are rare cancers. Around 3,300 people were diagnosed with soft tissue sarcoma in 2010 in the UK.[9]

The prevalence of soft tissue sarcoma in Europe has been quoted as 4 per 100,000[13] (adults only) and 30 per 100,000.[14]

About 2% of soft tissue sarcomas and 5·4% of cutaneous soft tissue sarcomas are angiosarcomas.[15]

Five year survival depends on the site of the angiosarcoma. Cancer Research UK reports five year survival as 30% overall, 65% for angiosarcoma of the breast, and 10% for major organs such as stomach or liver.[16]

According to HES data for England, there were 771 admissions in 2016-17 for 'malignant neoplasm: connective and soft tissue, unspecified' (ICD-10 C49.9) and 7,263 admissions for 'malignant neoplasm of other connective and soft tissue' (ICD-10 C49.0).[17]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Olaratumab in combination with doxorubicin for treating advanced soft tissue sarcoma (TA465). August 2017
- NICE technology appraisal. Trabectedin for the treatment of advanced soft tissue sarcoma (TA185). February 2010
- NICE guideline in development. NBTXR-3 for treating soft tissue sarcoma (ID1050, GID-TA10226). Expected publication date to be confirmed
- NICE guideline in development. Soft tissue or bone sarcoma (metastatic) - ridaforolimus (maintenance) (ID415, GID-TAG431). Expected publication date to be confirmed
- NICE guideline. Suspected cancer: recognition and referral (NG12). July 2017
- NICE cancer service guideline. Improving outcomes for people with sarcoma (CSG9). Last updated March 2014
- NICE quality standard. Sarcoma (QS78). January 2015
- NICE quality standard. Suspected cancer (QS124). Last updated December 2017.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: soft tissue sarcoma (adult). B12/S/a
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Children, Teenagers and Young Adults). B12/S/b
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a

OTHER GUIDANCE

- Andritsch E, Beishon M, Bielack S, Bonvalot S, Casali P, Crul M, et al. ECCO essential requirements for quality cancer care: soft tissue sarcoma in adults and bone sarcoma. A critical review (2017)[13]
- Dangoor A, Seddon B, Gerrand C, Grimer R, Whelan J, Judson I. UK guidelines for the management of soft tissue sarcomas (2016)[8]
- Lopez-Pousa A, Martin Broto J, Martinez Trufero J, Sevilla I, Valverde C, Alvarez R, et al. SEOM clinical guideline of management of soft-tissue sarcoma (2016)[18]
- von Mehren M, Randall RL, Benjamin RS, Boles S, Bui MM, Conrad EU, 3rd, et al. Soft Tissue Sarcoma, Version 2.2016, NCCN Clinical Practice Guidelines in Oncology (2016)[19]
- Garcia del Muro X, de Alava E, Artigas V, Bague S, Brana A, Cubedo R, et al. Clinical practice guidelines for the diagnosis and treatment of patients with soft tissue sarcoma by the Spanish group for research in sarcomas (GEIS) (2016)[20]
- Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2014)[21]

CURRENT TREATMENT OPTIONS

Surgery is the standard treatment to remove localised soft tissue sarcomas, often accompanied by pre- or post-operative radiotherapy. A specialist surgeon is required alongside a sarcoma multi-disciplinary team. [8]

Pazopanib is licensed for the treatment of adult patients with selective subtypes of advanced soft-tissue sarcoma (STS) who have received prior chemotherapy for metastatic disease, or who have progressed within 12 months after (neo) adjuvant therapy.[3] Where surgery is impossible or their disease does not respond to radiotherapy, NICE recommends treatment with olaratumab in combination with doxorubicin, or trabectedin.[22, 23]

EFFICACY and SAFETY

Trial	TAPPAS trial, NCT02979899; patients aged 12 or above; carotuximab (TRC105) in combination with pazopanib (Votrient) compared to single agent pazopanib; phase III
Sponsor	TRACON Pharmaceuticals, Inc.
Status	Ongoing
Source of Information	Poster[4], trial registry[2]
Location	EU (incl UK), USA
Design	Randomised, active-controlled
Participants	n=124 (planned); children, adults or seniors aged 12+ years (upper age limit not specified); angiosarcoma; disease that is metastatic, bulky or otherwise not amenable to surgery
Schedule	Randomised to 10 mg/kg TRC105 IV weekly in combination with 800mg (aged 18+) or 600mg (aged 12-17) pazopanib by mouth, once daily; or 800mg (aged 18+) or 600mg (aged 12-17) pazopanib by mouth, once daily
Follow-up	Active treatment until progression, death or patient withdrawal, follow-up 2 years
Primary Outcomes	Progression-free survival
Secondary Outcomes	Objective response rate, overall survival, adverse events (type, incidence, severity, timing, seriousness, and relatedness), patient-reported outcomes (using EQ-5D-5L and EORTC QLQ-C30), pharmacokinetic profile and immunogenicity
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as Dec 2019

ESTIMATED COST and IMPACT

COST

The cost of carotuximab is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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